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JACC STATE-OF-THE-ART REVIEW

Implantable Cardioverter Defibrillator and Resynchronization Therapy in Patients With Overt Chronic Kidney Disease

JACC State-of-the-Art Review

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ABSTRACT

Heart failure and chronic kidney disease are common and clinically important conditions that regularly coexist. Electrophysiologic changes of advanced heart failure often result in abnormal conduction, causing dyssynchronous contraction, and development of ventricular arrhythmias, which can lead to sudden cardiac arrest. In the last 2 decades, implantable cardioverter-defibrillator and cardiac resynchronization therapy devices have been developed to address these complications. However, when the coexisting chronic kidney disease is advanced, the associated pathophysiologic cardiovascular changes can alter the efficacy and safety of those interventions and complicate the management. This review explores the impact of comorbid advanced heart failure and advanced chronic kidney disease on the efficacy and safety of implantable cardioverter-defibrillator and cardiac resynchronization therapy, the currently available evidence, and potential future directions. (JACC. 2024;84:1342-1362) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation.

The structural and hemodynamic changes in heart failure (HF) can alter the cardiac conduction system and give rise to various electrical disturbances, including ventricular arrhythmias, atrial fibrillation, and electrical blocks. Although ventricular arrhythmias are often life-threatening medical emergencies that, if untreated, can end in sudden cardiac arrest (SCA) and death, conduction abnormalities may lead to dyssynchronous atrioventricular contraction and thereby result in worsening of an already impaired cardiac output. Cardiovascular implantable electronic devices (CIEDs), such as implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT), can be used in select patients as preventive and treatment modalities for these conditions. In many cases, the 2 devices, ICD and CRT, are combined as cardiac resynchronization therapy-defibrillator (CRT-D) to perform both tasks.

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HIGHLIGHTS

- The efficacy and safety of ICD and CRT devices have not been established for patients with advanced CKD, and available data suggest that they may be less favorable than in patients without advanced CKD.
- Factors limiting the effectiveness of these devices in patients with advanced CKD include the frequency of nonshockable arrhythmias, increased defibrillation thresholds, noncapture, myocardial fibrosis, coexisting atrial fibrillation, limited use of guideline-directed therapies for heart failure, and relatively high rates of nonarrhythmic mortality.
- Randomized trials are needed to improve selection of patients with advanced CKD for these device-based therapies.

The use of ICD for primary prevention of SCA in patients with symptomatic HF with a left ventricular ejection fraction (LVEF) below 35% is a Class I recommendation by American Heart Association/American College of Cardiology Foundation/Heart Failure Society of America guidelines and Class IIa recommendation by the latest European Society of Cardiology guidelines.[1,2] In addition, implantation of CRT devices in symptomatic HF patients with reduced LVEF and a prolonged QRS complex is a Class I recommendation by the American Heart Association/American College of Cardiology Foundation/Heart Failure Society of America and the European Society of Cardiology guidelines.[1,3] The current guidelines for both ICD and CRT devices stem from multiple randomized controlled trials (RCTs) demonstrating their efficacy in improving morbidity and mortality in patients with HF. The characteristics and results of the pivotal RCTs are summarized in **Table 1**. However, the utilization of these devices in patients with HF with certain comorbid conditions, such as advanced chronic kidney disease (CKD), is not as straightforward.

Although there are many relevant differences between patients with and without advanced CKD, which can result in dissimilar outcomes of device therapies, patients with advanced CKD have been excluded from the majority of the landmark studies.

This review focuses on the nephrocardiologic aspects of ICD and CRT, particularly emphasizing their utility in HF patients with advanced CKD. Furthermore, potential pathophysiologic mechanisms for altered device efficacy in patients with CKD are discussed.

CKD AS A COMORBIDITY IN HF

Due to the complex interaction of the renal and cardiovascular systems, HF and kidney failure frequently coexist. In fact, any patient with HF has some level of kidney dysfunction, whether apparent with a low estimated glomerular filtration rate (eGFR), or covert with a seemingly "normal" eGFR. Similarly, any patient with CKD has some degree of cardiac dysfunction, apparent or subclinical. Heart and kidney dysfunctions aggravate each other in a vicious cycle that involves several other factors such as hemodynamic alterations, neurohormonal dysregulations, inflammation and oxidative stress, metabolic irregularities, anemia, tissue ischemia, electrolyte abnormalities, acid-base disturbances, and malfunctioning of other organs, including the liver and intestine[4-6] (**Figure 1**). CKD, particularly in its advanced stages, is associated with various structural and functional cardiovascular abnormalities that can interfere with normal cardiac electrophysiology. Specifically, there is fibrosis and scarring of the myocardial tissue, atrial dilatation, ventricular hypertrophy, myocardial ischemia, increased myocardial tension caused by hypervolemia, electrolyte and acid-base abnormalities, high levels of uremic toxins, augmented sympathetic activity, and calcification of the vessels, valves, and myocardium (**Figure 2**). These factors are arrhythmogenic and can cause cardiac conduction abnormalities; hence, they are likely to interfere with the functions of ICD and CRT. Therefore, in patients with advanced stages of CKD, implantable devices may have different outcomes compared with those of HF patients without advanced CKD. However, patients with advanced CKD were either excluded or underrepresented in the pivotal randomized controlled trials of ICD and CRT. As a result, the utilization of these devices in patients with HF and advanced CKD has relied primarily on retrospective studies and subgroup analyses of RCTs.

Furthermore, it is important to note that, in addition to glomerular filtration rate (GFR), the serum level of creatinine is affected by several other factors, including the rate of the release of creatinine from the muscle cells into the bloodstream and the dilutional effect of patient's volume status, both of which often fluctuate in patients with HF. Therefore, the formulas

ABBREVIATIONS AND ACRONYMS

CIED = cardiovascular implantable electronic device

CKD = chronic kidney disease

CRT = cardiac resynchronization therapy

eGFR = estimated glomerular filtration rate

ESRD = end stage renal disease

HF = heart failure

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

RCT = randomized clinical trial

SCA = sudden cardiac arrest

TABLE 1 Randomized Controlled Trials for CRT and ICD in Patients With Heart Failure

Randomized Controlled Trial (Ref #)	Authors (Year)	Patient Population	Baseline Renal Function of Participants	Intervention Group	Control Group	Results
RCTs comparing ICD with control						
Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)[90]	Moss et al (2002)	1,232 patients with history of MI and LVEF <30%	Patients with ESRD were excluded Baseline BUN was >25 mg/dL in 29% of ICD group and 32% of control group Mean eGFR was 68.8 ± 23.9 mL/min/1.73 m^2 with eGFR <60 in 38% and <35 in 6.5%.[91]	ICD (n = 742)	Standard medical therapy (n = 490)	All-cause mortality was reduced in ICD group (14.2% vs 19.8%; $P = 0.016$) with an associated 31% relative reduction in risk of death from any cause in patients with ICD (HR: 0.69) Survival benefit in ICD group remained for an average follow-up time of 20 mo ($P = 0.007$)
Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE)[92]	Kadish et al (2004)	458 patients with NICM, LVEF <35%, and spontaneous PVCs or NSVT	Baseline renal function not reported	Standard medical therapy + single-chamber ICD (n = 229)	Standard medical therapy (n = 229)	Rate of all-cause mortality at 2 y: 14.1% in standard-therapy group, 7.9% in standard therapy with ICD group Substantial reduction in risk of arrhythmic death in ICD group (HR: 0.20; $P = 0.006$)
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[93]	Bardy et al (2005)	2,521 patients with ischemic or nonischemic HF in NYHA[a] functional class II or III and LVEF <35%	Excluded patients with creatinine >2.5 mg/dL Median baseline serum creatinine was 1.1 mg/dL in ICD, amiodarone, and placebo groups	Standard medical therapy + single-lead ICD (n = 829) Standard medical therapy + amiodarone (n = 845)	Standard medical therapy + placebo (n = 847)	No difference in all-cause mortality in amiodarone group vs placebo group (28% vs 29%; HR: 1.06; $P = 0.53$) All-cause mortality was 22% in ICD group vs 29% placebo group (HR: 0.77; $P = 0.007$) ICD therapy was associated with a 23% decrease in risk of death ($P = 0.007$) and absolute decrease in mortality of 7.2% after 5 y
Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure (DANISH)[94]	Køber et al (2016)	1,116 patients with nonischemic HF and LVEF <35% in NYHA functional class II or III	Patients with renal failure on dialysis were excluded. Baseline eGFR (mL/min/1.73 m^2) was 74 in ICD group (Q1-Q3: 58-91) and 73 in control group (Q1-Q3: 58-92)	ICD (n = 556) Note: 58% received CRT	Standard medical therapy (n = 560) Note: 58% received CRT	All-cause mortality was 21.6% in ICD group and 23.4% in control group ($P = 0.28$) Sudden cardiac death occurred in 4.3% of ICD group compared with 8.2% of control group (HR: 0.50; $P = 0.005$)
Cardiomyopathy Trial (CAT)[95]	Bänsch et al (2002)	104 patients in NYHA functional class II or III with recent onset of dilated cardiomyopathy (<9 mo) and LVEF <30%	Baseline renal function not reported	ICD (n = 50)	Standard medical therapy (n = 54)	2-, 4-, and 6-y survival was 93%, 80%, and 68% in the control group and 92%, 86%, and 73% in the ICD group (log-rank $P = 0.554$)

Continued on the next page

that estimate GFR based on a single serum creatinine measurement have serious limitations in this patient population. More importantly, a low GFR itself is not necessarily caused by CKD, because acute changes can also affect GFR. Moreover, those acute changes in GFR are not limited to intrinsic renal pathologies, because they can also be prerenal (ie, kidney hypoperfusion) or postrenal (ie, urinary tract obstruction), both of which are prevalent in the HF patient population. Therefore, despite what has been done in most, if not all, the previously published studies, estimating GFR based on a single serum creatinine measurement and translating that eGFR to a CKD stage, is an oversimplistic approach, which can result in imperfection of any conclusion that is drawn from such studies. In light of that, it should also be noted that because of those limitations of the published data, as well as the multitude and variability of the contributing factors, one cannot pinpoint a cutoff for CKD stage or eGFR that the discussed pathophysiologic mechanisms would apply. The structural and functional cardiovascular changes of CKD are a continuum that progresses with the advancement of CKD; thus, the clinician should individualize the

TABLE 1 Continued

Randomized Controlled Trial (Ref #)	Authors (Year)	Patient Population	Baseline Renal Function of Participants	Intervention Group	Control Group	Results
RCTs comparing CRT-D with ICD						
Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT)[96]	Moss et al (2009)	1,820 patients with ischemic or NICM, LVEF <30%, and NYHA functional class I or II symptoms. QRS complex duration was at least 130 ms	Patients with ESRD excluded Baseline serum creatinine was 1.2 ± 0.4 mg/dL in both groups Baseline BUN was >26 mg/dL in 24.5% of ICD group and 24.0% of CRT-D group	CRT-D (n = 1,089)	ICD (n = 731)	Death from any cause or nonfatal HF event occurred less frequently in CRT-D group (17.2% vs 25.3%; HR: 0.66; $P = 0.001$) and CRT-D was associated with a 41% reduction in risk of HF events Significant improvement in measurements of cardiac function in CRT-D vs ICD group, specifically for LVEF (+0.11 vs +0.03; $P < 0.001$), LVESV (−57 mL vs −18 mL; $P < 0.001$), and LVEDV (−52 mL vs −15 mL; $P < 0.001$)
Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT)[97]	Tang et al (2010)	1,798 patients with HF in NYHA functional class II or III, LVEF <30%, and intrinsic QRS complex >120 ms or paced QRS complex >200 ms	Baseline eGFR (mL/min/1.73 m^2) was <30 in 7%, between 30 and 59 in 42.7%, and >60 in 50.3% of ICD group Baseline eGFR (mL/min/1.73 m^2) was <30 in 6.4%, between 30 and 59 in 45.0%, and >60 in 48.6% of CRT-D group	CRT-D (n = 894)	ICD (n = 904)	The time until death was significantly delayed in CRT-D group (relative risk reduction 25%) Decreased all-cause mortality (20.8% vs 26.1%; $P < 0.001$) and death from cardiovascular cause (HR: 0.76) in CRT-D group HF hospitalizations occurred in 19.5% of CRT-D vs 26.1% of ICD groups ($P < 0.001$) Increased number of device-related hospitalizations (20% vs 12.2%; $P < 0.001$) and device-related complications (13.3% vs 6.8%; $P < 0.001$) in CRT-D group
RCTs comparing CRT-D to CRT-P						
Resynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE)[98]	Linde et al (2008)	610 patients with NYHA functional class I or II HF with QRS complex >120 ms and LVEF <40%	Patients with serum creatinine >3.0 mg/dL were excluded. Baseline eGFR (mL/min/1.73 m^2) was 89.6 ± 36.4 in CRT-OFF group and 84.2 ± 31.3 in CRT-ON group	CRT-D with active CRT and defibrillation (n = 419)	CRT-D with inactive CRT, active defibrillation (n = 191)	53% reduction in time-to-first HF hospitalization in CRT-ON group (HR: 0.47; $P = 0.03$) LVESVI decreased by 18.4 mL/m^2 in CRT-ON group vs 1.3 mL/m^2 in CRT-OFF group ($P < 0.0001$) Significant improvement in LVEF and LVEDVI observed in CRT-ON group
Multicenter InSync ICD Randomized Clinical Evaluation Trial (MIRACLE ICD)[99]	Young et al (2003)	369 patients with LVEF <35%, QRS complex >130 ms, and in NYHA functional class III or IV	Baseline renal function not reported Patients with serum creatinine >3.0 mg/dL were excluded	CRT-ON: CRT active, defibrillator active (n = 187)	CRT-OFF: CRT inactive, defibrillator active (n = 182)	Significant improvement in functional status in CRT-ON vs CRT-OFF group, as measured by median change in quality-of-life score (−17.5 points vs −11 points; $P = 0.02$), exercise duration (+55.5 s vs −11 s; $P < 0.001$), peak oxygen consumption (+1.1 vs +0.1 mL/kg/min; $P = 0.04$), and NYHA functional class (−1 vs 0; $P = 0.007$) at 6 mo

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decision making for patient care while considering the currently available evidence, which has been discussed here. Accordingly, in this review, the term "advanced CKD" has been used on many occasions, rather than a specific CKD stage or a certain eGFR.

Another consideration in safety and efficacy of CIED in advanced CKD is the potential complications

TABLE 1 Continued

Randomized Controlled Trial (Ref #)	Authors (Year)	Patient Population	Baseline Renal Function of Participants	Intervention Group	Control Group	Results
RCTs comparing CRT-D or CRT-P with control						
Cardiac Resynchronization - Heart Failure (CARE-HF)[100]	Cleland et al (2005)	813 patients with NYHA functional class III or IV HF, LVEF <35%, LVEDD >30 mm, and QRS complex >120 ms	Baseline eGFR (mL/min/1.73 m^2) was 60 in CRT group (Q1-Q3: 46-73) and 61 in control group (Q1-Q3: 46-73)	Standard medical therapy + CRT (n = 409)	Standard medical therapy (n = 404)	Significant decrease in all-cause mortality in CRT group (HR: 0.64; $P < 0.002$) Significant symptomatic improvement in CRT group, as evidenced by Euro Quality of Life[b] score (0.70 vs 0.63; $P < 0.001$) and NYHA functional class (2.1 vs 2.7; $P < 0.001$) at 90 d Significant improvement in LVESVI, interventricular conduction delay, and LVEF in CRT group at 18 mo ($P < 0.001$)
Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION)[101]	Bristow et al (2004)	1,520 patients with ischemic or NICM and LVEF <35%, NYHA functional class III or IV symptoms, and QRS complex interval >120 ms	Renal dysfunction was present in 23% of control group, 22% of CRT-P group, and 23% of CRT-D group.[102]	Optimal pharmacologic therapy with CRT-D (n = 595) Optimal pharmacologic therapy with CRT-P (n = 617)	Optimal pharmacologic therapy (n = 308)	Significant reduction in all-cause mortality in CRT-D group (HR: 0.64; $P = 0.003$) and CRT-P group (HR: 0.76; $P = 0.059$) Reduced risk of death or HF hospitalization at 12 mo in CRT-P group (HR: 0.66; $P = 0.002$) and CRT-D group (HR: 0.60; $P = <0.001$)

The safety and efficacy of cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) devices in heart failure patients was evaluated through multiple randomized clinical trials (RCTs). The characteristics of each study, including patient population, baseline renal function of participants, intervention and control therapies, and results, are listed above. The paucity of patients with advanced chronic kidney disease in these trials as well as the scarcity of reported information about kidney function is evident. Of note, some studies did not provide values for baseline renal function of participants. [a]NYHA classification of heart failure ranges from class I to IV, with higher class associated with more severe symptoms and severe functional limitations. [b]European Quality of Life-5 Dimensions instrument scores range from 0.594 to 1.000, with lower values consistent with a worsened quality of life.

BUN = blood urea nitrogen; CRT-D = cardiac resynchronization therapy with pacemaker-defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ESRD = end-stage renal disease; HF = heart failure; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; NICM = nonischemic cardiomyopathy; RCT = randomized controlled trial.

of those interventions. Although ICDs and CRTs effectively prevent SCA and restore synchronous ventricular conduction, respectively, the procedures to implant the devices are associated with short-term risks (ie, perforation, bleeding) and long-term complications (ie, infection, lead malfunction). Comorbidities such as advanced CKD can alter the incidence and severity of those complications. The presence of advanced CKD increases the risk of infection and hemorrhage. Further, percutaneous cardiovascular procedures can cause kidney damage, particularly when iodinated intravascular contrast agents are used.

Although both HF and CKD can trigger malignant ventricular tachyarrhythmias and conduction abnormalities, the type and severity of those conditions vary among individuals. Therefore, careful evaluation and risk stratification before implantation of ICD and CRT devices is essential. In this decision-making, many of the 9 elements of nephrocardiology, ie, pathophysiology, epidemiology, prevention, prognosis, diagnosis, therapy, monitoring, risk factors, and systemic diseases involving renal and cardiovascular systems, are applicable.[7,8]

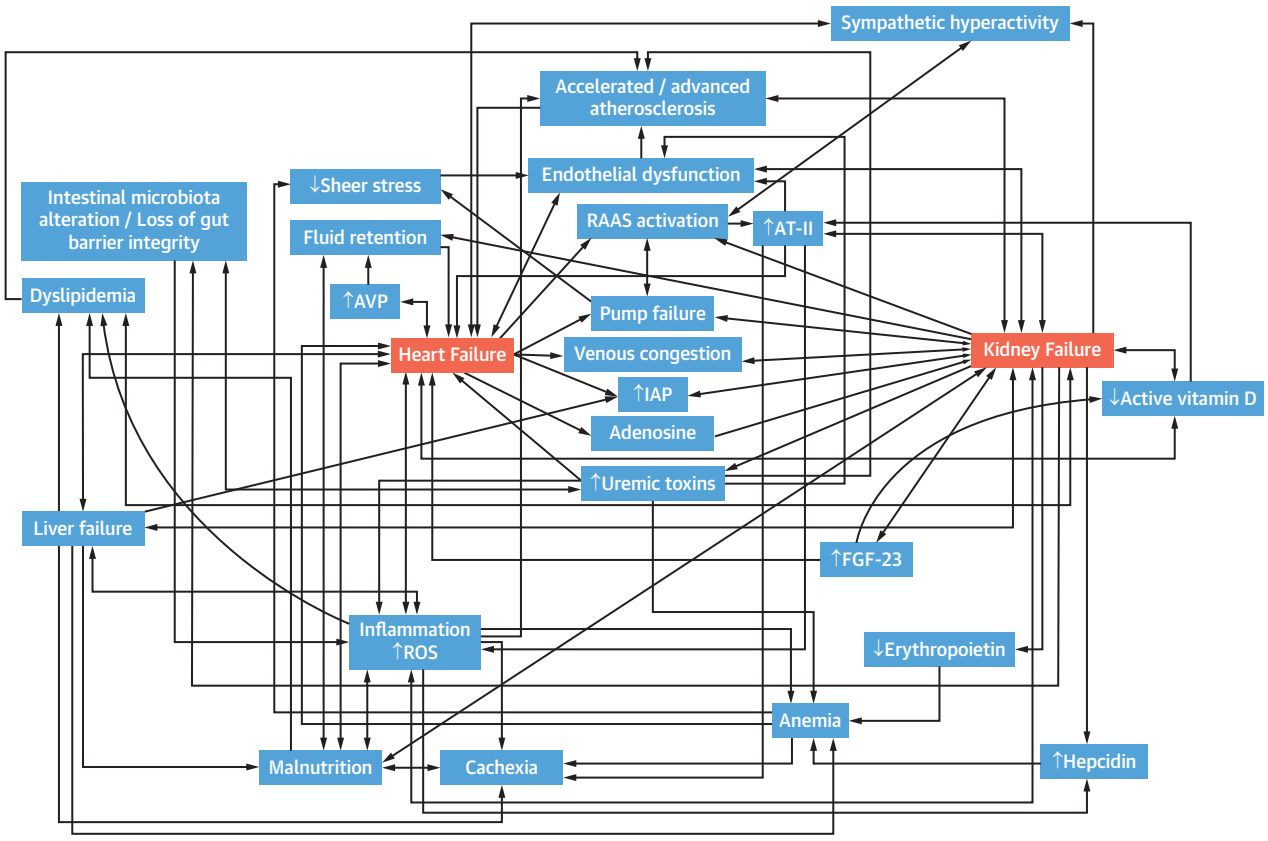
CIED OUTCOMES IN HF PATIENTS WITH ADVANCED CKD

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS.

Cardiovascular disease is the leading cause of death in CKD, with SCA accounting for 44% of mortality in end-stage renal disease (ESRD).[9] The risk for SCA increases as kidney function declines. Although ICD is an effective modality for the primary prevention of SCA in patients with HF, the landmark RCTs largely excluded patients with advanced CKD; therefore, it is unclear whether individuals with coexistent advanced CKD derive the same benefits.

Thus far, the evidence for the clinical outcomes of primary prevention ICD in HF patients with advanced CKD is limited (Table 2). A few retrospective cohort studies have shown increased morbidity and mortality postimplantation in patients with renal dysfunction. Chronic renal insufficiency is a robust independent predictor of mortality in ICD recipients, with an inverse association between the risk and the renal function.[10,11] For every 10-mL/min reduction in creatine clearance, there is a 55% increase in the risk of death.[11] Although the number of appropriate

FIGURE 1 Cardiorenal Pathophysiology



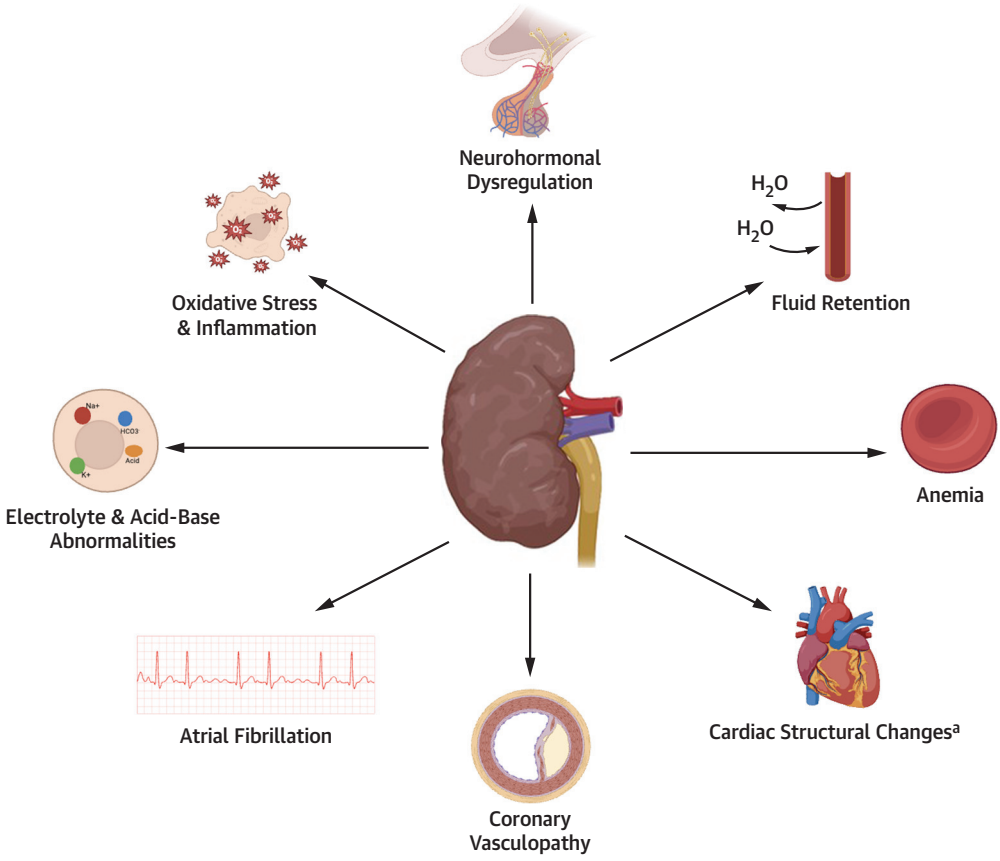
Heart and kidney malfunction exacerbate each other in a complicated network of events that involve multiple other contributing factors, including hemodynamic alterations, neurohormonal dysregulations, inflammation and oxidative stress, metabolic irregularities, anemia, tissue ischemia, electrolyte abnormalities, acid-base disturbances, and malfunctioning of other organs, including the liver and intestine. Reprinted from Hatamizadeh.[6] AT-II = angiotensin II; AVP = arginine vasopressin; FGF = fibroblast growth factor; IAP = intra-abdominal pressure; RAAS = renin-angiotensin-aldosterone system; ROS = reactive oxygen species.

shocks is higher in patients with CKD,[12] which indicates the presence of ventricular tachyarrhythmias in this population, the utilization of an ICD as primary prevention of SCA does not appear to provide a long-term survival benefit. In comparison to individuals without overt CKD, the outcomes of primary prevention ICD are poorer in patients with CKD, with a 1-year survival of 61.2% and 96.3% in patients with and without CKD, respectively.[11] Furthermore, a study by Bansal et al[13] found no significant difference in all-cause mortality between CKD patients in the ICD group compared with the non-ICD group, and there was an increased risk of hospitalization because of HF in patients who did receive an ICD.

In line with those findings, a meta-analysis of 3 randomized control trials (MADIT [Multicenter Automatic Defibrillator Implantation Trial]-I, MADIT-II, and SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial]) found a significant interaction between all-cause mortality after ICD implantation and eGFR. A survival benefit was noted in patients with eGFR ≥60 mL/min/1.73 m^2 (HR: 0.49) who received an ICD compared with standard care. However, no advantage was reported in patients with eGFR <60 mL/min/1.73 m^2.[14] This meta-analysis demonstrates that ICD efficacy may be attenuated as CKD severity increases. However, it is essential to note that the overall representation of patients with advanced CKD was low (3.6%) because the early RCTs largely excluded patients with kidney disease.

Although these studies primarily evaluated the safety and efficacy of transvenous ICD, the use of subcutaneous implantable cardioverter-defibrillators

FIGURE 2 Systemic Consequences of Chronic Kidney Disease



Chronic kidney disease is associated with several consequences that can affect the cardiovascular system, including the safety and efficacy of implantable cardioverter-defibrillator and cardiac resynchronization therapy. [a]Cardiac structural changes in patients with chronic kidney disease include myocardial fibrosis and scarring; calcification of vasculature, valves, and myocardium; ventricular hypertrophy; and capillary rarefaction. Illustration created in BioRender.com.

(S-ICDs) has become a favorable option in CKD patients, especially in dialysis-dependent renal failure. The periprocedural complication rate of S-ICD implantation was 2% in a study by Friedman et al,[15] which had a high proportion of patients with comorbid illnesses, including ESRD requiring dialysis. Nonetheless, renal dysfunction is also associated with conversion of S-ICD to transvenous ICD (OR: 2.67; $P = 0.008$) caused by a need for pacing or CRT functions at follow-up.[16] The newly emerged leadless pacemaker technology[17] may also become a potential option for patients with advanced CKD, including ESRD; however, it requires further studying.

CARDIAC RESYNCHRONIZATION THERAPY. Cardiac resynchronization therapy, a modality that can be used in HF patients with conduction abnormalities, is associated with improved morbidity and mortality, particularly in patients classified as responders. Although a universal definition for CRT responsiveness does not exist, studies have measured it in terms of all-cause mortality, HF hospitalizations, left ventricular (LV) structural and functional changes, and symptomatic improvement (eg, 6-minute walk test, NYHA functional class). Furthermore, post hoc and meta-analyses of the landmark CRT trials have investigated whether an interaction exists between certain baseline patient characteristics and outcomes. Hsu et al[18] investigated factors associated with super-response to CRT-D, defined as a change in LVEF in the top quartile, and its effect on morbidity and mortality among patients in the MADIT-CRT trial. Baseline predictors of super-response included intraventricular conduction abnormality with QRS complex

>150 ms, left bundle branch block, female sex, lack of prior myocardial infarction, body mass index <30 kg/m^2, and a smaller baseline left atrial volume index. Conversely, a meta-analysis of patients who received a CRT with pacemaker device in the CARE-HF (CArdiac REsynchronisation in Heart Failure) and COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trials did not reveal an independent relationship between QRS complex duration or morphology, or sex and the composite outcome of all-cause mortality and HF hospitalization. However, a greater mortality benefit was observed in patients with smaller stature or those on beta-blocker therapy.[19] The generalizability of these findings to HF patients with comorbid advanced CKD is unknown.

Retrospective studies have examined the effect of CRT on long-term outcomes in patients with CKD at various stages of the disease (**Table 3**). In a study by Höke et al,[20] there was a reduction in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) and an increase in LVEF among CKD stage 4 patients who received a resynchronization device in comparison to an ICD. Among CRT recipients, 30% were classified as responders, less than that in the average HF population. However, among those who experienced a positive response to CRT, defined as a ≥15% reduction in LVESV after 6 months, 62% had an improvement in eGFR, and responsiveness was associated with improved long-term outcomes, including overall survival, HF hospitalization, and defibrillation therapy. These beneficial outcomes are verified in a study by Friedman et al,[21] which revealed a lower 3-year incidence of hospitalization from HF or death in CKD stage 3 to 5 patients who received a CRT-D vs ICD alone (HR: 0.82; 95% CI: 0.75-0.90).

Although some CKD patients benefit from CRT, baseline renal function is an independent predictor of echocardiographic response and long-term mortality.[22,23] Reverse myocardial remodeling is observed across all stages of CKD; however, the percentage of responders is higher in lower stages of CKD, and the response is more pronounced in patients with closer to normal renal function.[22] A reanalysis of the REVERSE (Resynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) trial data that compared outcomes of CRT based on renal function revealed that the extent of LV structural and functional improvement was less in patients with overt CKD. Regardless of CRT, CKD was associated with decreased LV function, increased LV end-systolic and end-diastolic volumes and diameters, and worsened mitral regurgitation after adjustment for all confounders.[24] These results cannot be generalized to all stages of CKD, as the trial excluded patients with serum creatinine >3.0 mg/dL. In addition, renal responsiveness, characterized by an increase in eGFR, is associated with a reduced risk of all-cause mortality and HF hospitalization compared with patients without eGFR improvement.[22] Patients with stage 4 CKD at baseline appear to have higher renal response rates than stages 2 and 3, with only 14% of all patients but 28% of stage 4 patients exhibiting an improved eGFR postimplantation.[25] The value of eGFR at 6 months after initiation of resynchronization therapy is an independent predictor of mortality in advanced HF patients, and a more advanced CKD stage is associated with poorer outcomes, increasing the risk of 5-year death, heart transplantation, and LV assist device placement by 74.6%.[25,26] The association between eGFR and outcomes post-CRT implantation demonstrates the close interdependence of the heart and kidney with renal perfusion and filtering capacity increasing as cardiac function improves. The use of angiotensin-converting enzyme (ACEIs) inhibitors and angiotensin II receptor blockers, and the improvement of LVEF are independent predictors of renal response.[25] With renal response being a prognostic predictor of outcomes after the initiation of CRT, an important question is whether or not the overall survival can be augmented by initiating other therapies to improve kidney function. Although the renal response may be a marker of general well-being, which results in a better prognosis, given the close relationship between renal and cardiovascular systems, one can hypothesize that improving kidney function by other means, besides CRT, will also improve cardiovascular and overall outcomes.

Defibrillation capacity can be added to resynchronization devices (CRT-D) to protect against life-threatening ventricular arrhythmias. Adelstein et al[27] evaluated overall survival after appropriate defibrillation or antitachycardia pacing in CKD patients with CRT-D. The study found an independent negative association between eGFR and postshock mortality. After receiving any tachyarrhythmia therapy, 61% of patients died, with a median postshock survival of only 90 days for patients with eGFR <30 mL/min/1.73 m^2. These outcomes raise the question of whether CRT-D or any defibrillation device (ie, ICD) meaningfully prolongs life in patients with renal dysfunction. In contrast, Leyva et al[28] found CRT-D to be associated with a lower mortality risk and HF hospitalization than CRT without a

TABLE 2 Summary of Studies on ICD With Information About Kidney Function

Study (Year, Ref #)	Patient Population	Baseline Renal Function	Methodology	Findings
Cuculich et al (2007)[11]	229 patients who underwent ICD placement for primary prevention of SCD between 1999 and 2005	Normal renal function group (n = 194; mean LVEF 24.9%) and CKD group (n = 35; mean LVEF 25.4%) Creatinine clearance <30 mL/min in 20 patients, between 30-45 mL/min in 25 patients, between 45-60 mL/min in 41 patients, and >60 mL/min in 143 patients	Retrospective study Stratified patients according to CKD status (defined as serum creatinine >2 mg/dL or dialysis), and retrospectively compared outcomes in patients with and without CKD Primary endpoint(s): all-cause mortality Secondary endpoint(s): survival free of ICD therapy	1-y survival was 61.2% in CKD group vs 96.3% in non-CKD group ($P < 0.00001$) 5.5% increase in hazard of death with a decrease in creatine clearance by 1 mL/min Increased risk of death in patients with creatinine clearance <30 mL/min (aHR: 40.3; $P = 0.0001$) and 30-45 mL/min (aHR: 7.7; $P = 0.0001$) 28.6% of patients in CKD group vs 12.9% of patients in non-CKD group received ICD therapy during mean follow-up period of 18.0 ± 15.2 mo ($P = 0.018$) Time to first ICD therapy was 629 ± 107 d in CKD group and 1,806 ± 102 d in non-CKD group ($P = 0.0001$)
Chen-Scarabelli et al (2007)[10]	336 ICD patients followed in a clinic over previous 2.5 y 81.5% of all patients had an LVEF <30%, and 238 patients had ICM	111 patients with CRI (baseline creatinine >1.5 mg/dL) and 225 patients with normal renal function Mean creatinine of 2.2 ± 1.0 mg/dL in CRI group vs 1.13 ± 0.2 mg/dL in non-CRI group eGFR (mL/min/1.73 m^2) of 37.0 ± 10.6 in CRI group vs 71.9 ± 15.2 in non-CRI group	Retrospective study Compared outcomes of ICD therapy among patients with CRI (serum creatinine >1.5 mg/dL) and non-CRI Outcomes: VT, all-cause mortality	All-cause mortality of 11.1% in non-CRI group vs 32.4% in CRI group ($P < 0.0001$) in overall population All-cause mortality of 9.7% in non-CRI group vs 35.7% in CRI group ($P < 0.0001$) in ICM subgroup CRI increased the odds of VT in the ICM subgroup (OR: 1.95; $P = 0.03$), but not the overall population (OR: 1.36; $P = 0.25$) CRI was a predictor of mortality (OR: 2.75; $P = 0.003$) in both overall population and ICM subgroup
Bansal et al (2018)[13]	5,877 HF patients with LVEF <40% and CKD (defined as eGFR <60 mL/min/1.73 m^2), of whom 1,556 received an ICD and 4,321 did not, between 2005 and 2012	Mean eGFR of 43.5 mL/min/1.73 m^2 1.0% with eGFR (mL/min/1.73 m^2) <15, 13.8% between 15 and 29, 34.0% between 30 and 44, and 51.2% between 45 and 59 Excluded patients with ESRD	Retrospective study Patients with and without ICD were matched in a 1:3 ratio based on CKD status, age, and high-dimensional propensity score Mean follow-up was 3.1 ± 2.3 y Primary endpoints: all-cause mortality, HF hospitalization, any-cause hospitalization	All-cause mortality of 42.5% in non-ICD group vs 45.4% in ICD group (aHR: 0.96; $P = 0.04$) with adjustment for demographics, comorbidity, and cardiovascular medication use 25% higher relative risk of any-cause hospitalization in ICD group vs non-ICD group (aRR: 1.25) ICD associated with an increased risk of HF hospitalization (aRR: 1.49)
Pun et al (2014)[14]	2,867 HF patients from MADIT I, MADIT II, and SCD-HeFT trials with LVEF <35% and baseline renal functional available who received an ICD or standard care 1,533 patients received ICDs, and 1,334 patients received usual care	1,040 patients with eGFR <60 mL/min/1.73 m^2, and 1,827 patients with eGFR ≥60 mL/min/1.73 m^2 Mean eGFR of 45.4 mL/min/1.73 m^2 in patients in eGFR <60 mL/min/1.73 m^2 group 3.6% with eGFR <30 mL/min/1.73 m^2 No patients with ESRD	Meta-analysis of MADIT I, MADIT II, and SCD-HeFT trials eGFR was calculated at enrollment using CKD-EPI equation, and outcomes were compared among patients with eGFR ≥60 and <60 mL/min/1.73 m^2 Primary endpoint: all-cause mortality Secondary endpoints: re-hospitalization, ICD-related complications, arrhythmia-related death	Probability of death during average follow-up of 2.7 ± 1.5 y was 43.3% in non-ICD group vs 35.8% in ICD group Benefit of ICD on all-cause mortality decreased as eGFR declines (posterior probability $P < 0.001$) ICD was associated with decreased mortality in patients with eGFR ≥60 (aHR: 0.49), but the survival benefit was not observed in patients with eGFR between 30 and 59 mL/min/1.73 m^2 (aHR: 0.80) or <30 mL/min/1.73 m^2 (aHR; $P = 0.77$) Arrhythmia-related death was 35.0% and 23.8% in patients with eGFR ≥60 and <60 mL/min/1.73 m^2, respectively ($P = 0.002$) Significant reduction in arrhythmic death with ICD in patients with eGFR >60 mL/min/1.73 m^2 (HR: 0.22; $P = 0.001$), but no association observed in patients with eGFR <60 mL/min/1.73 m^2 (HR: 0.68; $P = 0.3$)

Continued on the next page

TABLE 2 Continued

Study (Year, Ref #)	Patient Population	Baseline Renal Function	Methodology	Findings
Studies on ESRD/Dialysis Patients				
Jukema et al (2019)[30]	188 patients with ESRD on dialysis with LVEF >35%, of whom 97 were in the ICD group and 91 were in the control group Trial was stopped after inclusion of 188 patients for futility reasons	All patients had ESRD on dialysis (hemodialysis or peritoneal dialysis)	Randomized controlled trial Patients were randomized in 1:1 fashion to receive an ICD or standard care Patients were followed for a mean duration of 6.8 y (Q1-Q3: 3.8-8.8 y) Primary endpoint: sudden cardiac (arrhythmic) death Secondary endpoints: all-cause mortality, device-related complications	5-y incidence of SCD was 9.7% in ICD group and 7.9% in control group (HR: 1.32; $P = 0.55$) 5-y survival probability was 50.6% in ICD group and 54.5% in control group (HR: 1.02; $P = 0.92$) Appropriate ICD therapy occurred in 13.8% of patients Adverse events occurred in 27.5% of patients who received an ICD, including hematoma in 2.5%, pocket infection in 3.8%, lead dysfunction in 12.5%, and device removal caused by bacteremia in 5.0%
Ayoub et al (2022)[40]	Patients from the nationwide inpatient sample database with ESRD (n = 14,363) and normal renal function (n = 28,172) who underwent ICD implantation between 2010 and 2016	Excluded patients with acute renal failure, history of renal transplant, and CKD without dialysis	Retrospective study Patients with ESRD and normal renal function were propensity matched (1:2) Outcomes were compared among patients with ESRD and normal renal function Outcomes: mechanical complications, hematoma, lead or pocket revision, vascular injury, pneumothorax, pericardial complications, blood transfusion, ICD infection, length of hospital stay, and in-hospital mortality	A higher risk of postprocedural complications in ESRD patients, including hemorrhage (OR: 1.67; $P < 0.0001$), blood transfusion (OR: 3.88; $P < 0.0001$), lead revision (OR: 1.24; $P = 0.035$), and vascular injury (OR: 2.02; $P = 0.0027$) Length of hospitalization was 11 d in ESRD vs 7 d in normal renal function ($P < 0.0001$) In-hospital mortality was higher in patients with ESRD (OR: 4.56; $P < 0.0001$) No significant difference in pericardial complications (OR: 1.9; $P < 0.18$) ESRD was associated with increased all-cause mortality (OR: 4.68; $P < 0.0001$)
Pun et al (2015)[29]	108 patients on chronic dialysis with documented HF and LVEF <35% who received primary prevention ICD between 2006 and 2007 195 patients on chronic dialysis with documented heart failure and LVEF <35% who did not receive an ICD between 2005 and 2009 Data was obtained from the National Cardiovascular Data Registry's ICD registry, the Centers for Medicare and Medicaid Services claims, and the Get With The Guidelines-Heart Failure database	Mean creatinine of 4.9 mg/dL in non-ICD group vs 4.1 mg/dL in ICD group Propensity-matched cohorts: mean creatinine of 3.9 mg/dL in non-ICD group vs 4.5 mg/dL in ICD group	Retrospective study Patients in ICD and non-ICD cohorts were propensity matched (1:1) Primary endpoint: all-cause mortality	1-y mortality rate of 42.2% and 38.1% in ICD cohort and non-ICD cohort, respectively 3-y mortality rate of 68.8% and 75.7% in ICD cohort and non-ICD cohort, respectively No difference in long-term mortality was observed (HR: 0.87; $P = 0.29$) Propensity matched cohorts: 1-y mortality rate of 43.4% in ICD cohort vs 39.7% in non-ICD cohort Propensity matched cohorts: 3-y mortality rate of 74.0% in ICD cohort vs 76.6% in non-ICD cohort No difference in long-term mortality was observed in propensity-matched groups (HR: 0.94; $P = 0.71$)

aHR = adjusted HR; aRR = adjusted relative risk; CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiological collaboration; CRI = chronic renal insufficiency; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; SCD = sudden cardiac death; VT = ventricular tachycardia.

defibrillator in patients with eGFR >60 and <60 mL/min/1.73 m^2. However, every 10 mL/min/1.73 m^2 decrease in eGFR was associated with a 15% higher risk of all-cause mortality.

OUTCOMES IN DIALYSIS PATIENTS. Patients on dialysis represent a high-risk population with unique intraoperative and postoperative needs. Despite the high rate of cardiovascular mortality attributable to SCA among hemodialysis patients, the outcomes of ICD and CRT remain suboptimal (Table 2). A propensity-matched study of 108 dialysis patients and 195 control subjects without primary prevention ICDs failed to show mortality benefits associated with

TABLE 3 Summary of Studies on CRT With Information About Kidney Function

Study (Year, Ref. #)	Patient Population	Baseline Renal Function	Methodology	Findings
Höke et al (2015)[20]	73 consecutive patients with stage 4 CKD and HF with LVEF <35% who received a CRT between 2000 and 2012 18 patients with stage 4 CKD and HF with LVEF <35% who received an ICD were selected as the control group	Excluded patients on hemodialysis, peritoneal dialysis, or kidney transplantation ICD group: eGFR of 24 ± 4 mL/min/1.73 m^2 and creatinine of 2.9 ± 2.1 mg/dL CRT group: eGFR of 25 ± 4 mL/min/1.73 m^2 and creatinine of 2.5 ± 0.5 mg/dL	Retrospective study Echocardiography and renal function studies were performed at baseline and 6-mo post-device implantation Patients were followed for a median time of 33 mo, and outcomes in CRT and ICD groups were compared CRT response was defined as ≥15% reduction in LVESV at 6-mo postimplantation Outcomes: HF hospitalization, all-cause mortality, and appropriate defibrillator therapy	NYHA[a] functional class improved from 3 to 2 in CRT group ($P < 0.001$) vs worsened from 2.5 to 3 ($P = 0.02$) in ICD group at 6 mo postimplantation eGFR improved from 25 ± 4 to 30 ± 9 in CRT group after 6 mo ($P < 0.001$), and the improvement was pronounced in CRT responders (25 ± 3 to 34 ± 9; $P < 0.001$) In CRT group, LVEDV improved from 205 ± 87 mL to 196 ± 85 mL, LVESV improved from 159 ± 78 mL to 145 ± 78 mL, and LVEF improved from 24 ± 8% to 28 ± 11% after 6 mo ($P < 0.05$) 30% of CRT patients were responders CRT responsiveness was associated with improvement in eGFR ($P < 0.001$), while no significant changes in eGFR were observed in CRT nonresponders ($P = 0.05$) and ICD groups ($P = 0.84$) Independent association between CRT responsiveness and an improved combined endpoint of HF hospitalization, defibrillator therapy, and all-cause mortality (HR: 0.51; $P = 0.04$)
Friedman et al (2015)[21]	10,946 patients with stage 3-5 CKD and LVEF <35% who received a CRT-D (n = 9,525) or ICD (n = 1,421) between 2006 and 2009 NCDR ICD Registry was used for patient selection—only patients ≥65 y of age on Medicare were included Chronic Conditions Warehouse database was used to assess outcomes and covariates (between 2005 and 2011)	CRT-D group: 49.6% in CKD stage 3a, 33.3% in stage 3b, 12.0% in stage 4, and 5.1% in stage 5 ICD group: 49.1% in CKD stage 3a, 31.2% in stage 3b, 11.8% in stage 4, and 7.8% in stage 5 4.4% and 7.0% of patients were on dialysis in CRT-D and ICD groups, respectively	Retrospective study Patients were followed for a median time of 30 mo, and outcomes were compared among CRT-D and ICD-only groups eGFR was calculated using the MDRD equation Primary outcome: HF hospitalization or death Secondary outcomes: HF hospitalization, death, progression to ESRD, device explant, and in-hospital and acute outpatient complications	3-y incidence of HF hospitalization or death was 57.2% in CRT-D group vs 45.0% in ICD group (HR: 0.72; $P < 0.001$) CRT-D associated with decreased risk of HF hospitalization or death (aHR: 0.82; $P < 0.0001$), death (aHR: 0.84; $P = 0.0019$), and HF hospitalization (aHR: 0.81; $P = 0.0003$)
Ter Maaten et al (2019)[22]	798 consecutive patients with HF undergoing CRT implantation between 2008 and 2016	Median eGFR of 62.8 mL/min/1.73 m^2 12.4% in CKD stage 1, 41.9% in stage 2, 33.6% in stage 3, 11.0% in stage 4, and 1.1% in stage 5	Retrospective study Renal function evaluated at baseline and 6 mo following implantation Echocardiography was performed to assess cardiac function CRT response was defined as a decrease in LVESV >15%, and renal response was defined as an increase in eGFR >10 mL/min/1.73 m^2 at 6 mo Patients were followed for a median time of 27 mo Endpoints: all-cause mortality and HF hospitalization, changes in LVEF, LVESV, and eGFR	CRT response: 78.2% of patients in stage 1, 76.0% in stage 2, 64.5% in stage 3, 61.0% in stage 4, and 50.0% in stage 5 LVEF improved by 15% in CKD stages 1-2 vs 10% in stages 3-5 ($P < 0.001$), and LVESV decreased by 37.2% in CKD stages 1-2 vs 29.9% in stages 3-5 ($P < 0.001$) Female sex, nonischemic HF etiology, and high dose neurohormonal blockade were associated with CRT response in CKD stages 3-5 ($P < 0.001$) Independent association between eGFR and echocardiographic response to CRT in all patients with CKD ($P = 0.023$) and in patients with CKD stages 3-5 ($P = 0.011$) LBBB ($P = 0.006$) and lower eGFR at baseline ($P < 0.001$) were independent predictors of renal function improvement at 6 mo Higher baseline eGFR was independently associated with a decreased risk of all-cause mortality or HF hospitalization (aHR: 0.8; $P = 0.013$) Patients with CKD stage 3-5 who experienced renal response to CRT had a reduced risk of all-cause mortality and HF hospitalization ($P = 0.007$) compared with patients without improvement in eGFR

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TABLE 3 Continued

Study (Year, Ref. #)	Patient Population	Baseline Renal Function	Methodology	Findings
Daly et al (2016)[23]	432 consecutive patients implanted with CRT-D between 2002 and 2011	CKD stages: stage 1 (n = 44), stage 2 (n = 162), stage 3 (n = 179), stage 4/5 (n = 30)	Retrospective study eGFR was calculated using MDRD equation, and patients were categorized into CKD stages 1-5 Patients were followed for a mean follow-up time of 4.3 ± 3.2 y Primary endpoint: all-cause mortality	5-y mortality of 36.3% for stage 1, 33.4% for stage 2, 40.6% for stage 3, and 62.1% for stages 4-5 ($P = 0.004$) Every 10 mL increase in eGFR was associated with a 6% decrease in mortality rate
Mathew et al (2012)[24]	561 patients from the REVERSE trial who were randomized to receive CRT or standard therapy	eGFR ≥60 mL/min/1.73 m^2 (n = 401) and eGFR <60 mL/min/1.73 m^2 (n = 160) Excluded patients with serum creatinine >3.0 mg/dL	Post hoc analysis of the REVERSE trial Categorized patients into CKD group (eGFR ≥ 60) and non-CKD group (eGFR <60) after calculating eGFR via CKD-EPI equation Compared CRT outcomes (echocardiographic parameters, heart failure clinical composite response) between groups over the course of 12 mo Primary outcomes: LV size and function, HF clinical composite response	Compared to non-CKD patients, CKD was associated with worsened LVEF (adjusted β coefficient, −1.80), LVESV (adjusted β coefficient, 14.16), LVEDV (adjusted β coefficient, 14.88), LVESD (adjusted β coefficient, 0.36), LVEDD (adjusted β coefficient, 0.24), mitral regurgitation (adjusted β coefficient, 3.12), and LV shape (adjusted β coefficient, 0.036) at 12 mo LVEF improved by 5.0% in non-CKD group vs 2.7% in CKD group ($P = 0.048$) LVEDV decreased by 38.9 mL in non-CKD group vs 22.9 mL in CKD group ($P = 0.045$) LVESV decreased by 37.8 mL in non-CKD group vs 21.3 mL in CKD group ($P = 0.019$) Mitral regurgitation decreased by 1.6% in non-CKD group vs increased by 2.0% in CKD group ($P = 0.026$)
Singal et al (2015)[25]	260 consecutive patients with CKD who underwent CRT implantation between 2003 and 2011	CKD stages: stage 2 (n = 67), stage 3 (n = 157), and stage 4 (n = 36) Excluded patients on dialysis and/or with eGFR >90 or <15 mL/min/1.73 m^2	Retrospective study eGFR was calculated using the MDRD equation Evaluated renal and cardiac function at baseline and 6-12 mo after implantation Renal response was defined as >10 mL/min/1.73 m^2 improvement in eGFR Primary endpoints: time to death, heart transplant, or LVAD Secondary endpoints: echocardiographic response, renal response	LVEF improved by 8.0 ± 10.5% in CKD stage 2, 5.7 ± 8.8% in stage 3, and 9.0 ± 11.1% in stage 4 ($P = 0.15$) 5-y event-free survival from death, transplant, or LVAD was 61.9% in CKD stage 2, 42.0% in stage 3, and 26.7% in stage 4 (log-rank $P >$ chi-square = 0.015) Renal response occurred in 27.8% of CKD patients in stage 4, 13.4% in stage 2, and 10.8% in stage 3 ($P = 0.03$) Use of ACEI/ARB was associated with a higher chance of renal response (OR: 4.31; $P = 0.039$) For every 1% increase in LVEF from baseline, there was a 6% increased chance of renal response (OR: 1.06; $P = 0.017$) A higher stage of CKD was associated with an increased likelihood of renal response (OR: 2.19; $P = 0.019$) 5-y event-free survival was 76.9% in renal responders vs 40.8% in non-renal responders ($P = 0.0396$), and 80% for renal responders with stage 4 CKD vs 0% for nonrenal responders with stage 4 CKD ($P = 0.02$) Renal response was associated with a 76% reduction in risk of death, heart transplant, or LVAD at 5-y post-implantation (HR: 0.24; $P = 0.011$)

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the ICD.[29] These results are substantiated by the ICD2 trial, which investigated the value and safety of ICD devices for primary prevention of SCA in patients with ESRD on dialysis and LVEF >35%. Despite 13.8% of patients in the ICD group receiving appropriate defibrillation for ventricular arrhythmias, the presence of an ICD did not reduce all-cause mortality, and the trial was subsequently stopped for futility reasons.[30]

The location of transvenous lead placement is an important consideration in hemodialysis patients undergoing transvenous CIED implantation.

TABLE 3 Continued

Study (Year, Ref. #)	Patient Population	Baseline Renal Function	Methodology	Findings
Gronda et al (2015)[26]	375 patients with HF who underwent CRT implantation between 1999 and 2009, among whom 277 patients received a CRT-D	Mean baseline eGFR was 59.9 ± 23.5 mL/min/1.73 m^2 52.7% of patients had CKD, defined as an eGFR ≤60 mL/min/1.73 m^2	Retrospective study Renal and cardiac function were evaluated at baseline and 6 mo postimplantation Baseline eGFR was calculated using MDRD equation CRT response was defined as an improvement in LVEF ≥10% at 6 mo postimplantation Patients were followed for a median of 43.0 mo Primary endpoint: all-cause mortality	Prevalence of CRT response was 36.3% With each 10-mL increase in baseline eGFR, there was a 12% decreased hazard of all-cause mortality (HR: 0.88; $P = 0.003$) With each 10-mL improvement in eGFR at 6 mo post-CRT implantation, there was a 14% reduced hazard of mortality (HR: 0.86; $P = 0.038$) CRT response was associated with a lower all-cause mortality (HR: 0.57)
Adelstein et al (2020)[27]	439 HF patients with LVEF <35%, QRS complex >130 ms, and non-RBBB pattern who were implanted with a CRT-D between 2000 and 2017, and received appropriate tachyarrhythmia device therapy (antitachycardia pacing or defibrillation)	Mean eGFR was 63 ± 23 mL/min/1.73 m^2 31 patients with eGFR ≤30, 164 with eGFR 31-60, and 244 with eGFR >60 mL/min/1.73 m^2	Retrospective study Baseline eGFR was calculated using MDRD equation Mean follow-up time was 64 mo post-CRT implant (Q1-Q3: 29-94 mo), and 32 mo after initial tachyarrhythmia therapy (Q1-Q3: 12-61 mo) CRT response was defined as an increase in LVEF ≥5% at 6 mo postimplantation Primary endpoint: mortality	Median time to initial shock was 19 mo for eGFR ≤30, 17 mo for eGFR 31-60, and 21 mo for eGFR >60 mL/min/1.73 m^2 ($P = 0.45$) Mortality after receiving an initial appropriate shock was 100% in patients with eGFR ≤30, 76% in eGFR 31-60, and 58% in eGFR >60 mL/min/1.73 m^2 during follow-up ($P < 0.001$) Median survival after initial defibrillation therapy was 90 d (95% CI: 0-233 d), 612 d (95% CI: 365-859 d), and 1,672 d (95% CI: 1,396-1,948 d) in patients with eGFR ≤30, 31-60, and >60 mL/min/1.73 m^2, respectively
Leyva et al (2019)[28]	1,046 patients undergoing CRT implantation, of whom 410 received CRT-D and 636 received CRT-P devices, between 2005 and 2017	Mean eGFR 57.1 ± 20.2 mL/min/1.73 m^2 57.2% of patients had an eGFR <60 and 42.8% had eGFR ≥60 mL/min/1.73 m^2	Retrospective study Baseline eGFR was calculated using MDRD equation Outcomes were compared among patients with eGFR ≥60 and <60 mL/min/1.73 m^2, and device type Patients were followed for a median of 3.7 y (Q1-Q3: 2.1-5.7 y) in eGFR <60 mL/min/1.73 m^2 group and 3.9 y (Q1-Q3: 2.2-6.0 y) in eGFR mL/min/1.73 m^2 ≥60 group Primary endpoint: all-cause mortality Secondary endpoints: cardiac mortality (heart transplantation or LVAD), total mortality or HF hospitalization, total mortality or hospitalization for MACE MACE included HF, myocardial infarction, acute coronary syndrome, and arrhythmia	All-cause mortality was 45.7% in eGFR <60 mL/min/1.73 m^2 group vs 33.2% in eGFR ≥60 mL/min/1.73 m^2 group Patients with eGFR <60 mL/min/1.73 m^2 had a greater risk of all-cause mortality (aHR: 1.28; $P = 0.017$), total mortality or HF hospitalization (aHR: 1.32; $P = 0.004$), cardiac mortality (aHR: 1.33; $P = 0.036$), and total mortality or hospitalization for MACE (aHR: 1.34; $P = 0.002$) compared with the eGFR ≥60 mL/min/1.73 m^2 group CRT-D was associated with a decreased risk of all-cause mortality in eGFR ≥60 mL/min/1.73 m^2 group (aHR: 0.65; $P = 0.028$) and eGFR <60 mL/min/1.73 m^2 group (aHR: 0.64; $P = 0.0002$) compared with CRT-P Each 10-mL/min/1.73 m^2 decrease in eGFR was associated with a 15% higher risk of all-cause mortality

[a]NYHA Classification of Heart Failure ranges from Class I to IV, with higher class associated with more severe symptoms and severe functional limitations.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LBBB = left bundle branch block; LVAD = left ventricular assist device; MACE = major adverse cardiovascular events; MDRD = modification of diet in renal disease; NCDR = National Cardiovascular Data Registry; RBBB = right bundle branch block; other abbreviations as in Tables 1 and 2.

Transvenous leads are associated with central vein stenosis with the frequency of severe stenosis and occlusion ranging from 11% to 36%.[31-33] In hemodialysis patients, there appears to be a higher incidence of central vein stenosis, particularly when the arteriovenous fistula (AVF) and transvenous lead are positioned ipsilaterally. In a study by Teruya et al,[34] symptomatic central vein stenosis occurred in 71% of patients on hemodialysis on average 12.6 months after AVF formation, which was created ipsilaterally to the CIED in all patients. As such, AVF and transvenous leads should be positioned contralaterally when possible. However, the availability of vascular sites and frequency of AVF revision caused by poor patency can present clinical challenges to successfully obtaining contralateral placement. Importantly, the use of a central venous catheter for hemodialysis represents the highest risk for central vein stenosis

and infection-related complications.[35,36] Moreover, from a nephrology standpoint, vein preservation strategies are important in ESRD patients because their longevity may depend on the availability of vascular sites for hemodialysis. Thus, when placing an intravenous lead in an ESRD patient or a patient who is expected to become dialysis-dependent at some point in life, one should consider the risk of central venous stenosis and the resultant challenges of finding a dialysis vascular access in the future. Other options for CIED therapy, such as a subcutaneous ICD, or a transition to peritoneal dialysis should be considered in select patients.[37] In a subgroup analysis of hemodialysis patients from the subcutaneous ICD postapproval study, there was no significant difference in 1-year complication rates between dialysis and nondialysis patients (7.9% vs 7.7%; $P = 0.9169$).[38] However, the frequency of inappropriate shocks and appropriate shocks was higher in dialysis patients ($P = 0.0137$ and $P = 0.0003$, respectively),[38] likely related to electrolyte disturbances and altered hemodynamics in this high-risk cohort.[39]

COMPLICATIONS ASSOCIATED WITH CIED IMPLANTATION. Patients with renal dysfunction, especially in advanced stages, have an increased risk of procedure-related complications. In a propensity-matched study, ESRD was associated with a higher odds of postoperative hemorrhage, blood transfusion requirements, and mechanical complications necessitating lead revision.[40] Furthermore, in addition to longer hospitalization, there was a higher in-hospital mortality in patients with ESRD.[40,41] The increased rate of adverse events can be attributed, at least in part, to the prevalence of comorbid illnesses in this patient cohort. As mentioned previously, patients on hemodialysis are among the highest risk for complications, particularly device infections because of the frequency of vascular access or presence of indwelling catheters,[42] as well as impaired cellular immune function.[43] The incidence of CIED infection in hemodialysis patients is over 3 times greater than the general population.[44] Charytan et al[45] found a postimplantation infection rate of 988 events per 1,000 patient-years during the first year after the procedure. The presence of comorbidities complicates device extraction, and as such, extraction was only performed in approximately 27% of ESRD patients with device infection, despite a 25% reduction in overall mortality associated with device extraction compared with antimicrobial therapy alone.[44] The management of device infection in patients with renal dysfunction warrants additional research.

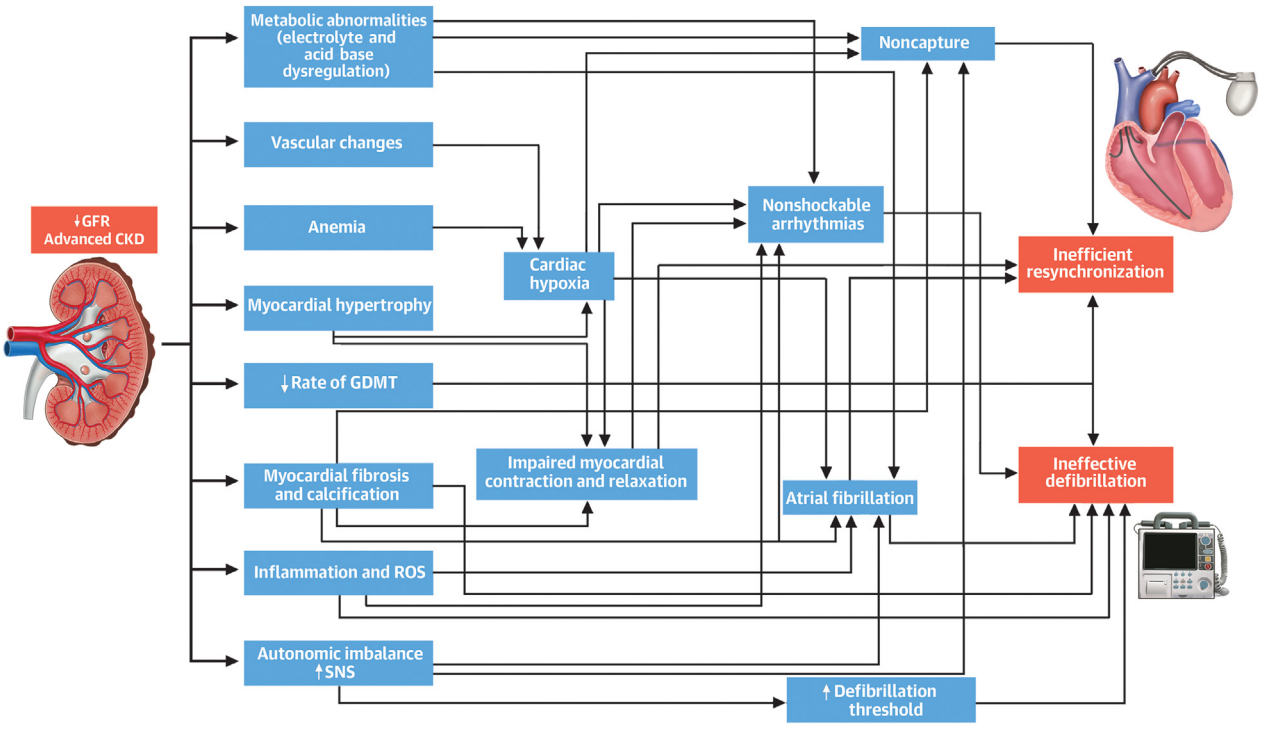
POTENTIAL PATHOPHYSIOLOGICAL MECHANISMS FOR DECREASED RESPONSIVENESS TO ICD AND CRT IN ADVANCED CKD

Even though patients with overt CKD receive a greater number of appropriate defibrillation impulses from the ICD, there is an attenuated mortality advantage in comparison to the general patient population. Similarly, the beneficial effects of CRT appear to be diminished in the presence of an evident comorbid CKD. The following pathophysiologic mechanisms can be postulated for these attenuated responses (**Central Illustration**).

DIFFERENT ARRHYTHMIA MECHANISMS. An explanation for the decreased survival benefit of ICD could be the presence of other rhythm disturbances, such as bradyarrhythmias, that do not respond to defibrillation. This is the reason that some experts have speculated that the ICDs which have pacing function may be more beneficial in this patient population.[46] Wong et al[46] utilized implantable cardiac monitors (ICMs) in 50 hemodialysis patients with LVEF >35% to prospectively evaluate the long-term incidence and timing of arrhythmias in hemodialysis patients. Arrhythmia events occurred in 86% of patients, and 16% experienced SCA. At the time of SCA, the underlying rhythm on ICM was severe bradycardia with asystole in all cases. Arrhythmia events not associated with SCA included bradycardia (30%), sinus arrest (28%), second-degree atrioventricular block (8%), nonsustained ventricular tachycardia (20%), and paroxysmal atrial fibrillation (28%). The long interdialytic period was the highest risk time period for rhythm abnormalities, likely caused by metabolic, electrolyte, acid-base, and fluid abnormalities. Asystole as a potential mechanism of SCA was also found in a study by Wan et al,[47] which evaluated the survival and characteristics of SCA in hemodialysis patients using wearable cardioverter defibrillators. Ventricular tachycardia or fibrillation and asystole were the causes of cardiac arrest in 78.6% and 21.4% of patients, respectively, with a decreased survival associated with asystole, given the lack of a shockable rhythm.

HIGHER DEFIBRILLATION THRESHOLD AND NONCAPTURE. Another contributing factor to the decreased efficacy of ICD and CRT in patients with overt CKD is a higher defibrillation threshold and loss of electrical capture. Noncapture, which is the failure of the myocardium to respond to electrical stimuli from devices, has both cardiac and noncardiac causes. Long-term causes of noncapture include fibrosis,

CENTRAL ILLUSTRATION **Putative Mechanisms for Impaired Efficacy of ICD and CRT in CKD**



Varga CR, et al. JACC. 2024;84(14):1342–1362.

The favorable effect of ICD and CRT appears to be diminished in the presence of comorbid advanced CKD. Potential contributing factors include high prevalence of nonshockable arrhythmias; increased defibrillation threshold and noncapture caused by multiple mechanisms, including the extensive myocardial scar tissue; coexisting atrial fibrillation; lower rate of GDMT; and nonarrhythmic causes of death. The illustration shows the network of events that can result in lower efficacy of ICD and CRT in this patient population. ↑ indicates increase; ↓, decrease. CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; GDMT = guideline directed medical therapy; GFR = glomerular filtration rate; ICD = implantable cardioverter defibrillator; ROS = reactive oxygen species; SNS = sympathetic nervous stimulus.

inflammation, cardiomyopathy, electrolyte imbalances, acidemia, and hypoxemia.[48] In addition, heightened sympathetic and diminished parasympathetic activity can increase the defibrillation threshold.

The sympathetic nervous system activity is enhanced in CKD, which is implicated in arrhythmogenesis and defibrillation thresholds. Cardiac injury can result in increased sympathetic activation and withdrawn parasympathetic input. This state of autonomic imbalance with a dominant sympathetic tone reduces the ventricular refractory period and ventricular fibrillation threshold, ultimately promoting triggered activity and automaticity.[49] Furthermore, nerve growth factor is upregulated in cardiac hypertrophy, a common finding in CKD, resulting in sympathetic hyperinnervation.[49,50] Under normal conditions, heightened sympathetic activity can be suppressed by feedback to the central nervous system through baroreceptors. However, baroreceptor sensitivity is reduced in CKD stages 4 and 5.[51] Baroreceptor sensitivity impairment is a prognostic factor for mortality and SCA.[10,49] Decreased parasympathetic activity in the setting of HF and kidney disease can negatively affect cardiac devices, specifically those with defibrillation capacity. Morillo et al[52] modulated the autonomic nervous system pharmacologically with muscarinic agonists or reflexively through baroreceptors, and found that the defibrillation threshold decreased and the ventricular fibrillation threshold increased with parasympathetic stimulation. This demonstrates that autonomic balance, especially parasympathetic tone, has a role in arrhythmogenesis and device efficacy.

Metabolic changes, which are highly prevalent in CKD, can also impair electrical capture and alter

defibrillation thresholds. Hyperkalemia is the most common electrolyte imbalance associated with loss of device capture, although other electrolyte abnormalities can also cause it.[53,54] This is initially caused by an increased threshold; however, as potassium levels continue to rise, the QRS complex widens, and the T-wave increases in amplitude, leading to oversensing and a decreased pacing frequency.[48] Hypoxia and acidemia can also alter device thresholds, promoting a loss of capture.[48] Although acidemia occurs because of a reduced ability of the kidneys to reabsorb bicarbonate and excrete acids, cardiac hypoxia can occur through a few mechanisms in CKD. First, perivascular deposition of fibrotic tissue in the myocardium can impair oxygen diffusion.[55] In addition, vascular calcification can lead to microvascular disease and compression of coronary arteries.[56] Furthermore, myocardial hypertrophy and capillary rarefaction decrease the availability of microcirculation.[57,58] Last, erythropoietin synthesis in the kidneys is decreased, which, along with other effects of a uremic milieu, results in CKD-associated anemia and diminished oxygen delivery.[59]

Failure to terminate lethal arrhythmias because of an increased defibrillation threshold and inability to stimulate myocardium for resynchronization effectively because of noncapture likely contribute to the decreased benefits of ICD and CRT-D in patients with CKD.

INCREASED MYOCARDIAL FIBROSIS AND SCARRING. Myocardial fibrosis negatively affects cardiovascular outcomes and prognosis in patients with CKD.[55] Myocardial fibrosis is characterized by diffuse collagen deposition between capillaries and cardiomyocytes caused by pathological activation of cardiac fibroblasts and myofibroblasts. The deposition of excess extracellular matrix can lead to maladaptive ventricular remodeling and impaired mechanoelectrical coupling, ultimately leading to the induction and progression of HF.[56,60] CKD can further augment this pathological process because of multiple profibrotic factors, including altered hemodynamics, neurohormonal activation, inflammation, oxidative stress, mineral and electrolyte abnormalities, and uremic toxins.[55]

Both renal dysfunction and HF contribute to an expanded intravascular volume through chronic activation of the renin-angiotensin-aldosterone system, stimulated by decreased glomerular filtration and effective circulating volume. Although initially a beneficial compensatory mechanism in HF to maintain organ perfusion, the chronic up-regulation of angiotensin II and aldosterone can lead to ventricular fibrosis and subsequently increase the overall workload of the heart because of peripheral vasoconstriction and elevated afterload.

Angiotensin II is a central effector molecule in cardiac fibroblast proliferation, migration, collagen synthesis, and inflammation.[60] Specifically, activating the angiotensin II type 1 receptor increases the expression of transforming growth factor-β, a proinflammatory cytokine that is an essential mediator in angiotensin II–induced myocardial hypertrophy and fibrosis.[60-62] Nevertheless, the profibrotic effect of angiotensin II is not limited to cardiac tissue. Matrix deposition in the renal parenchyma in patients with CKD is observed, progressively reducing renal function.[63]

The abundance of fibrotic scar tissue in the myocardium of CKD patients may contribute to the decreased efficacy of ICD and CRT, because scar tissue reduces the amount of excitable myocardium available for the pacing stimulus. This effect appears to be more prominent when the device leads happen to be placed within the fibrotic scar tissue. A clinical trial by de Roest et al[64] evaluated whether there was a benefit to avoiding scar tissue when placing the LV lead of CRT devices in patients with ischemic cardiomyopathy. Stimulation of scar tissue, irrespective of location, led to pump function deterioration. An increase in baseline mean stroke work was observed when the pacing location was moved from an area of scar tissue to viable myocardium.[64] The improvement in LV function was inversely related to the amount of LV scar tissue.

Indeed, impaired device efficacy in fibrosis and inflammation may be attributable to loss of capture.[48] The presence of scar tissue at the pacing site is associated with increased QRS complex duration and fragmentation, leading to incomplete resynchronization and suboptimal response to CRT.[65] Lead repositioning to areas of scar-free myocardium using safe methods in patients with advanced CKD can be a potential strategy that requires further studying.

In addition to interference with cardiac excitability and electrical activity, myocardial fibrosis, calcification, hypertrophy, and scarring that are common in advanced CKD,[56,66,67] can impair ventricular relaxation and contractility and result in regional and global wall motion abnormalities. The latter further diminishes the beneficial effects of CRT by impairing the harmonized contraction of the affected areas of myocardium.

In a study of 65,000 patients who underwent CRT implantation, earlier initiation of CRT in the course of HF was associated with a lower mortality and the combined endpoint of mortality or HF hospitalization.[68] Higher burden of fibrosis and permanent

scarring of myocardial, renal, and perhaps other organ tissues in later stages likely contribute to the worse outcome. Given the fact that renal responsiveness is positively associated with morbidity and mortality, renal fibrosis may indirectly decrease device efficacy in patients with CKD. Moreover, by providing hemodynamic support, earlier commencement of CRT can result in better adherence to guideline-directed medical therapy for HF,[69] including the renin-angiotensin-aldosterone system antagonists, which can further delay the process of fibrosis and scarring and improve overall prognosis.

COMORBID ATRIAL FIBRILLATION. Atrial fibrillation (AF) is prevalent in patients with renal dysfunction. According to a subanalysis of the ARIC (Atherosclerosis Risk In Communities) study, in comparison to individuals with eGFR ≥90 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio <30 mg/g, patients with eGFR 15 to 30 mL/min/1.73 m^2 and macroalbuminuria (urine albumin-to-creatinine ratio ≥300 mg/g) had a markedly increased risk of AF (HR: 13.1).[70] Guo et al[71] reported a 4-fold increase in the prevalence of AF in a population of individuals with CKD vs without CKD and found that a lower eGFR value was associated with an increased risk of incident AF. These findings are supported by a post hoc analysis of the REGARDS (REasons for Geographic and Racial Differences in Stroke) study, a population-based cohort of African-American and Caucasian adults over the age of 45 years in the United States, which revealed a differential prevalence of AF according to CKD stage. The prevalence of AF was 1.0%, 2.8%, 2.7%, and 4.2% in participants without CKD and with stages 1 to 2, 3, and 4 to 5 CKD, respectively.[72]

In a cohort of 1,064 hospitalized patients with AF, comorbid CKD was associated with increased risk of all-cause (adjusted HR [aHR]: 1.60) and cardiovascular mortality (aHR: 1.74).[73] Moreover, incident AF in patients with CKD increases the rate of progression to ESRD by 67%,[74] highlighting the bidirectional interaction between AF and CKD.

Potential contributory factors for the development of incident AF in patients with CKD include electrolyte abnormalities, uremic toxins, reactive oxygen species, chronic inflammation, enhanced sympathetic activity, volume overload, and myocardial fibrosis. Chronic inflammation is postulated to be involved in the pathogenesis of AF in the general population, as evidenced by an elevated serum C-reactive protein in both paroxysmal and persistent AF patients compared with those in normal sinus rhythm.[75] This is particularly relevant to patients with CKD, because the sequelae of downstream systemic effects of progressive renal dysfunction precipitates a state of chronic inflammation. In fact, an elevated C-reactive protein is a risk factor for the development of incident AF in the CKD population.[71,72] The accumulation of uremic toxins in CKD contributes to inflammation and oxidative stress, as well as actuates change in myocardial baseline electrical activity, all of which have implications in arrhythmogenesis. Indoxyl sulfate, a uremic toxin, has been shown to cause calcium leak in the pulmonary veins and induce delayed afterdepolarizations, shorten left atrial action potential duration, and increase burst firing within the pulmonary veins,[76] which are electrophysiological changes that can predispose to atrial fibrillation. Furthermore, the inducibility and duration of AF is increased in the presence of indoxyl sulfate.[76]

Myocardial fibrosis and left atrial stretch can also lead to the development of AF by promoting arrhythmogenesis through deposition of fibrotic tissue or volume overload, respectively. The level of extracellular signal-related kinases and ACE in cardiac tissue is elevated in patients with AF vs sinus rhythm with an associated marked atrial fibrosis in those who have increased kinase expression.[77] This ACE-dependent increase in kinases leading to atrial fibrosis and AF may be further exacerbated in patients with CKD, who already have an up-regulation of the renin-angiotensin-aldosterone system, and thereby contribute to the increased prevalence of comorbid AF in this population.

Although limited data exists on the impact of CRT and ICD in patients with AF and CKD in comparison to those with sinus rhythm and CKD, the potential negative influence of comorbid AF on device efficacy can be ascertained from studies on patients with AF who received CRT or ICD. A meta-analysis that included 63,282 patients by Mustafa et al[78] found that ICD patients with AF were at a greater risk of all-cause mortality (OR: 2.11; $P < 0.001$) and appropriate shock therapy (OR: 1.77; $P < 0.001$) than those in normal sinus rhythm. Of note, a survival benefit from ICD therapy compared with conventional pharmacologic therapy was not observed in patients with AF (OR: 0.69; $P = 0.12$).[78] Conversely, 1-year mortality was similar among CRT patients with AF and those with normal sinus rhythm.[79] Although the average change in LVEF was slightly greater, CRT patients with AF experienced less benefit in functional outcomes, as indicated by a smaller improvement in the 6-minute walk test and Minnesota Living With Heart Failure questionnaire score.[79] Based on these findings, the diminished effects of ICD and CRT in patients with CKD can be attributed, at least in some individuals, to an underlying comorbid AF, especially considering the increased prevalence of AF in CKD.

LOWER RATE OF GUIDELINE-DIRECTED MEDICAL THERAPY. Guidelines recommend implantation of ICD and CRT devices in patients who have been optimized on medical therapy for at least 3 months.[1] However, pharmacologic treatment of HF can be difficult in the setting of CKD, because many of the medications utilize renal clearance, requiring dose adjustments, and target aspects of renin-angiotensin system, which can further exacerbate renal dysfunction and increase adverse effects.[80] As a result, patients with comorbid CKD and HF have lower adherence to guideline-directed medical therapy (GDMT). In a retrospective analysis of patients hospitalized with HF, the use of ACEIs and angiotensin receptor blockers was decreased in patients with severe renal impairment (GFR <15 mL/min) compared with patients with normal renal function (GFR >90 mL/min) during hospitalization (52.0% vs 69.5%; $P < 0.0001$) and at discharge (50.5% vs 65.1%; $P < 0.0001$).[81] Even without an established contraindication or intolerance, nearly one-third of advanced CKD patients were not optimized on medical therapy.[82]

The use of GDMT in conjunction with implantable devices confers a greater mortality benefit. With each additional GDMT medication, the risk of death was reduced by 30% in patients who received a CRT-D (HR: 0.70; $P < 0.001$) and by 36% in patients who received an ICD (HR: 0.64; $P < 0.001$).[83] Furthermore, at 6 months post-CRT implantation, patients classified as responders were more likely to be on ACEI/angiotensin receptor blocker (94% vs 84%; $P = 0.01$) at a higher mean daily dosage (85% vs 76% of target dose; $P = 0.009$) and receive a lower dose of diuretic agents (60 vs 90 mg/d furosemide equivalent; $P < 0.001$) compared with nonresponders.[69] Given the independent association between use of incremental GDMT and all-cause mortality in patients with implantable devices, the decreased adherence to GDMT in patients with advanced CKD may contribute to the impaired efficacy of CRT and ICD in this patient population.

NONARRHYTHMIC CAUSES OF CARDIOVASCULAR DEATH. The worsened mortality associated with ICD and CRT-D implantation in patients with overt CKD compared with the general population raises an essential question regarding the underlying mechanism of sudden cardiac death. Although patients with CKD are exposed to various factors, including myocardial fibrosis and electrolyte abnormalities, which can provoke ventricular tachyarrhythmias, other nonarrhythmic processes may precipitate cardiovascular death in these patients. An abundance of evidence has shown that the severity of CKD is associated with the risk of noncardiovascular and cardiovascular death, including those caused by nonarrhythmic etiologies. Patients in the most advanced stage of CKD have a 6.5 times hazard of nonarrhythmic cardiovascular and noncardiovascular death.[84] Furthermore, the predominant cause of death in severe HF is a nonarrhythmic etiology, which is exaggerated in the presence of more advanced CKD. Therefore, the benefits of defibrillation devices in HF patients with comorbid CKD may be limited by the high prevalence of nonarrhythmic mortality.

Traditional cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes, are highly prevalent in CKD. Elevated levels of triglycerides and decreased high-density lipoprotein (HDL) are observed in patients with CKD. With progressive kidney dysfunction, the composition of HDL becomes more atherogenic because of increased oxidative stress, proinflammatory molecules, and uremic toxins, ultimately increasing the risk of coronary disease.[56] Furthermore, hyperphosphatemia, a prevalent electrolyte abnormality in CKD, is associated with vascular calcification and coronary atherosclerosis.[51] Medial calcification of arteries and perivascular fibrosis can impair cardiac function by decreasing perfusion.[55,56] Vascular calcification also increases cardiac afterload, which may precipitate acute pump failure in patients with advanced stages of HF and CKD.[56] Additionally, ventricular hypertrophy and diastolic dysfunction are common in advanced CKD, as are valvular heart diseases.[56,66,67,85] Therefore, nonarrhythmic cardiovascular mortality caused by systolic and diastolic HF, as well as those related to myocardial ischemia and valvular heart disease, is common in patients with advanced CKD. Moreover, CKD patients have a higher risk of noncardiovascular mortality from malnutrition, infection, and cancer.[86-89]

CONCLUSIONS

Overall, the studies on CRT in patients with CKD reveal a potential long-term benefit, specifically in responders, with an association between renal responsiveness and cardiac responsiveness. The outcomes of devices with defibrillation capacity, whether a CRT-D or an ICD, are not as clear. However, the consensus leans toward no difference or worse outcomes with defibrillation devices. Nonetheless, the efficacy of both modalities appears to be attenuated in the presence of advanced CKD, indicating that there may be competing pathophysiological processes. Potential explanations include the following: 1) nonshockable arrhythmias; 2) increased

defibrillation threshold and noncapture; 3) abundance of myocardial scar tissue; 4) coexisting atrial fibrillation; 5) lower rate of GDMT; and 6) nonarrhythmic mortality.

When evaluating patients with HF for appropriateness of ICD or CRT implantation, the stage of CKD and potential reversibility of HF and CKD-associated conditions (volume abnormalities, electrolyte and acid-base disturbances, cardiac structural abnormalities, etc) must be considered as essential factors in decision making. To that end, it is very important to distinguish between a "real CKD," which is associated with irreversible functional and structural changes of the kidney and the heart, and an elevated serum creatinine caused by reasons other than CKD that may represent a different pathophysiology.

Randomized trials focusing on CRT and ICD in patients with HF and advanced CKD are necessary to assess the risks and benefits in this population. Furthermore, a closer look at potential mediators of the efficacy and safety of ICD and CRT in the setting of advanced CKD might help modify our approach with the devices. These mediators include electrolyte and acid-base abnormalities, volume dysregulations, uremic toxin levels, autonomic nervous imbalance, myocardial hypertrophy and fibrosis, atrial fibrillation, device lead placement, adequate medical therapy, and device parameters.

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